DETAILED ACTION

1a. Applicants' response filed on 02 July 2008 is acknowledged.

Status of Claims:

1b. Claims 28-36 and 38-40 are pending and under consideration.

Information Disclosure Statement:

2. The information disclosure statement (IDS) submitted 02 July 2008 was received and complies with the provisions of 37 CFR §1.97 and §1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Claim Rejections - 35 U.S.C. §101/112, first paragraph:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 28-36 and 38-40 stand rejected under 35 U.S.C. 101/112, 1st, because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility. Claims 28-36 and 38-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not

know how to use the claimed invention. See the office actions mailed on 03/04/2008, 11/29/2004, 06/07/2007 and 05/13/2004.

The claims are directed to an isolated polypeptide comprising at least 80% to 99% to the amino acid sequence set forth in SEQ ID NO:77, with or without its signal peptide, or comprising the amino acid sequence of the full-length coding sequence of the cDNA deposited under ATCC accession number 203292, wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors. Claims are also presented to chimeric proteins comprising the aforementioned polypeptides. It is noted that the phrase "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumor" is not an activity limitation for the claimed polypeptides; rather, it is a characteristic of a nucleic acid. In other words, the claims do not require that the claimed polypeptides be overexpressed in any tumor, or have any biological activity.

Applicants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. The specification discloses that the gene encoding PRO1293 was amplified in one primary lung tumor (HF-000840) and two colon tumors, (HF:000539, and HF-000795), (see page 503, column 1). The specification teaches that HF-000840 is a primary lung tumor and that HF-000539 and HF-000795 are colon tumor “centers”, (see page 507, lines 5-12). However, there is no description of the type of lung tumor (adenocarcinoma or squamous, cell carcinoma or large cell carcinoma for example) or colon tumor or what cancer stage were these samples. The specification provides no details regarding the

types or stages of lung or colon tumors these samples are, such information is provided for other tumors at page 499, table 7.

The specification asserts that gene amplification is associated with over-expression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung and other cancers, (page 494, lines 20-25). The specification also generally asserts that the polypeptides are useful as diagnostics for cancer. However, the instant specification does not demonstrate that the PRO1293 polypeptide is actually overly expressed in any of the cancers mentioned. Applicants have not shown that there is a relationship between DNA amplification and increased amounts of corresponding mRNA, protein or antibody. Although the data in the instant specification shows that gene copy number is increased in certain tumor tissue samples, it does not necessarily follow that an increase in gene copy (DNA) number results in increased gene expression (mRNA) and increased protein expression, such that the polypeptide of SEQ ID NO:77, or antibodies that bind it, would be useful diagnostically or as target for cancer drug development. In order for PRO1293 polypeptides to be overexpressed in lung or colon tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed.

35 U.S.C. § 112, first paragraph (Written Description):

3b. Claims 28-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a polypeptide having at least 80%, 85%, 90%, 95%, 99% sequence identity to a the polypeptide of SEQ ID NO: 77, or the polypeptide of SEQ ID NO:77 lacking its associated signal peptide, wherein the nucleic acid encoding the polypeptide is over-expressed in colon or lung tumor cells. However, the specification teaches only the structure of the polypeptide of SEQ IDNO: 77 wherein the nucleic acid encoding the polypeptide is over-expressed in colon or lung tumor cells (see office actions). Applicant has not described or shown possession of all polypeptides 80%, 85%, 90%, 95%, and 99% homologous to SEQ ID NO: 77, that still retain the function of SEQ ID NO:77. Nor has Applicant described a representative number of species that have 80%, 85%, 90%, 95%, and 99% homology to SEQ ID NO: 77, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 77.

Response to Applicants' Arguments:

4. Applicants submit that the PTO has not established a prima facie case for lack of utility and that the polypeptides of claims 28-36 and 38-40 possess a specific and substantial asserted utility, and that based upon this utility, one of skill in the art would know how to use the claimed polypeptides without any further experimentation. Applicants submit that the gene amplification data disclosed in Example 143 establishes a credible, substantial and specific patentable utility for the PR01293 polypeptides and

antibodies that bind them, and the gene amplification data for the gene encoding the PRO 1293 polypeptide is clearly disclosed in the instant specification under Example 143. Applicants argue that as previously discussed, ΔCt value of at least 1.0 was observed for PRO1293 in at least three of the tumors listed in Table 8. PRO1293 showed approximately 1.71 ΔCt units which corresponds to $2^{1.7l}$ fold amplification or 3.27 fold amplification in primary lung tumor (HF-000840), and approximately 1.13-2.33 ΔCt units which corresponds to $2^{1.13}$ -2 $^{2.33}$ fold amplification or 2.19 fold to 5.03-fold amplification in colon tumors (HF-000539 and HF-000795).

On pages 3-6, Applicants argue that they have submitted ample evidence to show that in general, if gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For instance, the articles by Orntoft et al., Hyman el al., and Pollack el al. (submitted with Response of September 9, 2004) collectively teach that in general, gene amplification increases mRNA expression. Applicants also submit that the Goddard and the two Polakis Declarations, teach that in general there is a correlation between mRNA levels and polypeptide levels. Applicants further submit that even if there were no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility, because as evidenced by the Ashkenazi Declaration and the teachings of Hanna et al. (made of record in the Response submitted September 9, 2004), simultaneous testing of gene amplification and gene product over- expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to

better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu. Applicants argue that taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, as exemplified by the teachings of Orntofl et al., Hyman et al., Pollack et al., and the Polakis Declaration, the art in general overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO 1293 gene, that the PRO 1293 polypeptide is concomitantly overexpressed and has utility in the diagnosis of lung and colon cancers.

Applicant's arguments have been fully considered but are not found to be persuasive. In the instant case, the specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue (lung and colon). However, there is no evidence regarding whether or not PRO 1293 mRNA or polypeptide levels are also increased in these cancers. Further research needs to be done to determine whether the small increase in PRO1293 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested the instant disclosure. It is not known whether PRO1293 is expressed in corresponding normal tissues, and what the relative levels of expression are. Therefore, it is not clear that the reported amplification is significant. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1293 is

amplified in a variety of samples and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete (see Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689)). With respect to Applicants' argument that the PRO1293 of the instant invention is useful as in tumor prognosis, the specification does not disclose such further testing of gene product overexpression. Therefore, the skilled artisan would have been required to do the testing to reasonably confirm whether or not the PRO1293 polypeptide is overexpressed. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public. Furthermore, the specification provides no assertion that the claimed PRO1293 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO1293. For example, neither the specification nor the prior art discloses an antagonists against PRO1293 that is useful for cancer therapy. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial.

As discussed in the previous Office Action and reiterated herein, the declaration under 37 C.F.R. § 1.132 by Dr. Goddard was fully considered in the Office Action of 29 November 2004. The Examiner maintains that the Goddard declaration is not pertinent, as it is drawn to the significance of the amplification of the nucleic acids, and fails to address the issue of the claimed polypeptides, which are encoded by the nucleic acid which is alleged to be significantly amplified in cancer. Furthermore, the Declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Goddard's conclusions are provided in the declaration. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (cited in the Office Action of 25 April 2005) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Therefore, the Goddard declaration is not persuasive as it relates only to the issue of nucleic acid and not to the claimed subject matter, which is polypeptides, and further, the claims were directed to nucleic acids, would still have not been persuasive.

Likewise, the Declaration of Dr. Polakis, filed under 37 CFR 1.132 (09 September 2004), is insufficient to overcome the rejection of claims 28-36 and 38-40, based upon, 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action because: In the Declaration filed under 37 CFR 1.132 (09 September 2004), staff scientist Ashkenazi claims that the purpose of the experiments that measured increases in gene copy number was to identify tumor cell markers useful for cancer treatment and to identify cancers for which there was an absence of gene product over-expression. The Ashkenazi declaration filed under 37 CFR § 1.132 argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment.

This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial. The Polakis declarations pertain to the correlation between mRNA levels and protein levels, however, they do not speak to whether or not amplified genomic DNA levels correlate with increased levels of the encoded proteins. The claims under examination are directed to antibodies that bind the polypeptide of SEQ ID NO:77, and Applicants have not shown that amplification of the genomic DNA encoding PRO1293 in lung and colon tumor samples, results in amplification of the polypeptide. With respect to the Polakis Declarations filed by Applicant, in assessing the

weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paraqon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.19 fold to 5.03-fold amplification of the gene encoding PRO1293 in two lung tumors and one colon tumor is significant. The significance can be questioned based on the absence of factual support for the expert's opinion. In the instant case, the facts are that eleven of the fourteen lung tumor samples did not show an amplification of the gene encoding PRO1293, and the control used was not a matched non-tumor lung or non-tumor colon sample but rather was a pooled DNA sample from blood of healthy subjects.

On pages 6-7, Applicants submit that the Examiner's position is incorrect because the instant application relies on genomic DNA amplification for utility and not cDNA expression. Different types of cells from the same organism should have the same set of genomic DNA. Thus, it does not matter what kind of cells you use for the control as long as the control cells have the entire genome. Applicants argue that a "tissue-matched" control is not necessary in the gene amplification assay. Applicants further point out that Pennica et al. teaches the exact same "pooled normal blood controls" as that used in the instant gene amplification assay (for instance, see page

14718, column 1 and Figure 5 of Pennica et al.). Applicant contends that Pennica et al. use the same control for their gene amplification experiments as that described in the instant specification. Applicant submits that Pitti et al. (submitted with the Response of 07 August 2006) describe the analysis of DNA copy number in genomic DNA from primary tumors relative to pooled genomic DNA from peripheral blood leukocytes. Applicant argues that Bieche et al. (submitted with the Response of 07 August 2006) used normal leukocyte DNA derived from a small subset of breast cancer patients and note that the results of the study are consistent with those reported in the literature. Applicant concludes that the art demonstrates that pooled normal blood samples are considered to be a valid negative control for gene amplification experiments.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, although Pennica et al. and Pitti et al. compare gene amplification of specific genes in colon and lung tumors to pooled DNA from 10 healthy normal donors, Pennica et al. and Pitti et al. are not attempting to utilize the data generated from the experiments for diagnostic purposes (as is Example 143 of the instant application). Secondly, Bieche et al. is simply utilizing real-time PCR to validate an assay for the detection and determination of the copy numbers of the three most frequently amplified genes in breast tumors (myc, ccndl, and erbB2). Bieche et al. compare the results for 108 breast tumors with previous Southern-blot data for the same samples (abstract; page 662, column 1). The genes studied by Bieche et al. were already well-known in the art to be amplified in breast cancer. Thus, it was not necessary to utilize matched normal tissue samples. Regarding the instant application,

the specification provides data purportedly showing a slight increase in DNA copy number in three different types of tumor tissue (lung and colon) of PRO1293. However, PRO1293 is novel and has not been characterized in the pre- or post-filing date art. It is not known whether PRO1293 is expressed in corresponding normal tissues, and what the relative levels of expression are. There is no structure/function analysis in the specification regarding the putative protein encoded by the PRO1293 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner cannot find any reason to suspect, that the protein encoded by the PRO1293 gene would confer any selective advantage on a cell expressing it. It has no known homology to any protein that would be expected to confer a selective advantage to a tumor cell. Additionally, gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Therefore, data pertaining to PRO1293 genomic DNA do not indicate anything significant regarding the claimed PRO1293 polypeptides. The data do not support the specification's assertion that PRO1293 polypeptides and their antibodies can be used as cancer diagnostic agents. Significant further research would have been required of the skilled artisan to reasonably confirm that the PRO1293 polypeptide is overexpressed in any cancer to the extent that the polypeptide or antibodies that bind it could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO1293 polypeptide levels are also different between

specific cancerous and normal tissues, the proposed use of the PRO1293 polypeptides and antibodies as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides and antibodies.

At pages .8-10, Applicant argues that the gene amplification was not due to aneuploidy. Applicant also points to the Ashkenazi declaration as showing that gene amplification is still useful for cancer diagnosis even if the determination includes chromosomal aneuploidy. Referring to Sen and Hittelman, Applicant agrees that aneuploidy can be a feature of damaged tissue and may not invariably lead to cancer. However, Applicant reasons that PRO1293 is still useful in diagnosing pre-cancerous lesions or cancer itself. Applicant urges that the prior art is consistent with this view.

This has been fully considered but is not found to be persuasive. The specification does not assert that the PRO1293 polypeptides or antibodies are useful as diagnostic markers for damaged epithelial tissues. The specification clearly asserts that the markers are for cancer diagnosis and cancer therapeutic drug development only. Therefore, Applicant's arguments are in contradiction to the asserted utility in the specification and, in fact, support the rejections.

At pages 10-12, Applicant argues that a prima facie case of lack of utility has not been established. Applicant urges that the proper legal standard is "more likely than not" rather than "necessarily." Applicant criticizes Pennica et al. as being limited to individual WISP genes, and that no general trends can be concluded therefrom. Applicant points to the correlation between WISP-1 gene amplification and polypeptide

overexpression. Applicant also takes issue with the Konopka et al. reference, again urging that Konopka et al. is limited to a single gene, and teach nothing regarding the correlation between gene amplification and protein expression levels in general.

This has been fully considered but is not found to be persuasive. The instant application also presents data from a single gene at a time and makes conclusions about gene products from genomic DNA data. Pennica et al. constitutes evidence that it cannot be assumed that amplified genomic DNA for a single gene results in overexpressed gene product. Godbout et al. and Li et al. also provide evidence to this effect with respect to the general concept of whether or not gene amplification correlates with increased mRNA/polypeptide expression. Finally, Sen constitutes evidence that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer.

At pages 14-15 Applicant criticizes Li et al. Applicant urges that Li et al. acknowledge that their results differed from those of Hyman et al. and Pollack et al., and note that the difference may be due to different methodologies. Applicant refers to the supplemental information accompanying the Li et al. article, enclosed. Applicant urges that Li et al. used an amplification copy ratio of only 1.4, which is not significant according to the Goddard declaration, and that a copy number of at least 2 was necessary and that the instant PRO1293 gene showed 2.19 fold to 5.03 amplification in adenocarcinoma as or squamous cell carcinomas of the lung and colon, which meets this standard.

This has been fully considered but is not found to be persuasive. First, it is noted that Hyman et al. also found that less than half of the amplified genes were overexpressed at the mRNA level, even though they only investigated genes in genomic DNA regions that were amplified at least 2-fold, and thus Hyman et al. supports the examiner's position. Furthermore, Li et al. did not limit their studies to genes that were amplified at less than 2-fold. In fact, the supplemental information indicates that some of the samples were required to bind with a probe requiring at least 2-fold amplification:

> Genes with copy number ratio > 1.40 (representing the upper 5% of the CGH ratios across all experiments) were considered to be overrepresented. A genomic fragment that contained six or more adjacent probes showing a copy number ratio > 1.40, or a region with at least three adjacent probes with a copy number ratio > 1.40 and no less than one probe with a ratio > 2.0, were considered to be amplicons. (emphasis added, from 1s* page of supplemental material).

At pages 15-17, Applicant argues that it is "more likely than not" for amplified genes to have increased mRNA and protein levels. Applicant refers to Orntoft et al., Hyman et al., and Pollack et al. as evidencing that, in general, gene amplification increases mRNA expression.

This has been fully considered but is not found to be persuasive. Orntoft et al. could only compare the levels of about 40 well resolved and focused abundant proteins," (See abstract). It would appear that Applicant has provided no fact or evidence concerning a correlation between the specification's disclosure of low levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded polypeptide. Hyman et al. found 44% of highly amplified genes showed overexpression at the mRNA level, and 10.5% of highly overexpressed genes were amplified; thus, even at the level of high

amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1293 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, Hyman et al. supports the basis of the rejections that it is more likely than not that gene amplification fails to correlate with increased mRNA/polypeptide levels. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. Furthermore, it is interesting to note that Pollack et al. found correlations in their breast cancer samples, but referred to another investigative group that found very poor correlations in colon cancer samples. See bottom of right column of p. 12967 of Pollack et al. wherein they discuss Platzer et al. Also interesting is that Pollack et al. used a normal female leukocyte DNA control from a single donor rather than normal breast tissue (matched tissue control), whereas Platzer et al. compared colon cancer samples to normal colon epithelium. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung or colon cancer.

At page 19, Applicant argues that ample evidence has been submitted in terms of references and declarations that support the argument that, in general a change in mRNA expression level for a particular gene leads to corresponding change in the level of expression of the encoded protein . Applicant urges that the publications evidence

that it is more likely than not that gene amplification correlates well with protein over-expression, and that such would be accepted as reasonable and credible by one in the art. Applicant urges that the "more likely than not" standard is lower than the "accurate" or "necessary" standard.

This has been fully considered but is not found to be persuasive because it is inaccurate. The rejection discusses each publication and other piece of evidence brought forth on the record regarding this issue and has concluded, based on the preponderance of the totality of the evidence, that it is more likely than not that gene amplification fails to correlate with protein over-expression. Patentable utility must be credible, specific, and substantial. Credibility and specificity have not been questioned. However, the asserted utility is not substantial because it would require further research to reasonably confirm a real world use. The rejection is supported by several pieces of evidence that show that gene amplification cannot be assumed to correlate with protein overexpression. See Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., Li et al., Hanna and Mornin, and the Ashkenazi declaration. Since the priority filing date of September 1998, no evidence has been brought forth on the record as to whether or not the polypeptide level of PRO1293 was tested in normal and cancerous tissue, and thus the skilled artisan must perform additional experiments, as directed by the art. Since the asserted utility for the claimed polypeptides is not in currently available form, and further experimentation is required to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

At pages 19-20, Applicant takes issue with the Godbout et al. reference. Applicant argues that Godbout et al. evidences the good correlation between gene amplification and protein expression levels.

This has been fully considered but is not found to be persuasive. As discussed above, the art indicates that only those amplified genes which confer a selective advantage on the cell is overexpressed in cancer cells. Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) state "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." (emphasis added). The polypeptide encoded by the DDX gene had been characterized as being a putative RNA helicase, a type of enzyme that would be expected to confer a selective advantage to the cells in which it (the DDX gene) was amplified. Contrary to Appellant's characterization of the reference, on page 21167, right column, first full paragraph, Godbout et al. state "It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region

(GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO1293 confers any selective growth advantage to a cell, and thus it cannot be presumed that the PRO1293 polypeptide is overexpressed because the genomic DNA including the gene being studied is amplified.

Finally, the teachings of the cited references have been acknowledged by the examiner. However, none of the cited references address the major issue in this rejection, which is whether or not the PRO1293 gene amplification in lung and colon tumor leads to overexpression of the PRO1293 polypeptide in said tumors. Applicant has not established if the disclosed amplification of the PRO1293 gene is one of those cases wherein the PRO1293 polypeptide is overexpressed. Applicants have not tested PRO1293 mRNA expression. Applicant has not tested PRO1293 polypeptide expression. Gene expression is, admittedly, quite complicated. Hanna, Pennica and Konopka suffice to show that that DNA amplification is not always associated with overexpression of the gene product. This art, as well as the Sen, Hittelman, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the claimed polypeptides have utility and enablement based on a presumption of overexpression in view of gene amplification data. In the absence of information regarding whether or not PRO1293 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1293

polypeptides and antibodies as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion ."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., and Li et al.), the rejection of claims 28-36 and 38-40 made under 35 U.S.C. 101/112, 1st , is properly maintained.

35 U.S.C. § 112, first paragraph (Written Description):

3b. Claims 28-32 stand rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description.

Applicant argues that the same position set forth in the previous responses that claims 28-32 satisfy the written description requirement under 35 U.S.C. 112, first paragraph is maintained.

This is considered but is not deemed persuasive. Claims 28-32 fail to satisfy the written description requirement under 35 U.S.C. 112, first paragraph for reason of record set forth in the previous offices action mailed on 05/13/2004, 11/21/2004, 04/03/2006, 06/01/2007 and 04 March 2008. Thus, the Examiner maintains the same

position as set forth in said office actions, (especially see the office action mailed on 01 June 2007).

Conclusion:

5. No claim is allowed.

No new rejections have been made. THUS, ***THIS ACTION IS MADE FINAL.*** However, since new publications have been cited to support the maintained rejections, Applicant is assured that any new evidence specifically addressing the Hittelman, Sen, Fleischhacker, Godbout et al or Li et al references will be entered after final and given full consideration. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FOZIA M. HAMUD whose telephone number is (571)272-0884. The examiner can normally be reached on Monday-Friday: 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fozia Hamud
Patent Examiner
Art Unit 1647
17 October 2008

/Manjunath N. Rao, /

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